II. REMARKS

Claims 2-11 and 14-16 are pending. Claims 2-6, 8, 9, 11, 14 and 15 are amended. No new matter is added. Reconsideration in view of the amendments and remarks is respectfully requested.

I. Maintained Rejections

A. Claims 2-5, 8, 9, 11 and 14-16 are rejected under 35 U.S.C. § 102

Claims 2-5, 8, 9, 11 and 14-16 are rejected under 35 U.S.C. § 102 as being anticipated by Walker et al. 1994, Pirttila et al. 1994, WO200162801, and Naslund et al. 2005. Applicants respectfully traverse the rejection.

Claim 2 is directed to a monoclonal antibody that specifically recognizes the first 5 to 7 human amino acids of the β-secretase_11 cleavage site of Aβ, which is Aβ11-15 (EVHHQ) and Aβ11-17 (EVHHQKI) or the first 5 to 7 mouse amino acids of the β-secretase_11 cleavage site, which is Aβ11-15 (EVRHQ) and Aβ11-17 (EVRHQKL). The antibody as set forth in claim 2 has specificity to Aβ11-x peptides and no cross-reactivity to full length Aβ1-40/42 peptide. Claims 3-5 depend on claim 2. Claim 8 is directed to a method for determination or detection of Aβ11-x peptides with the monoclonal antibody of claim 2. Claim 15 is directed to a diagnostic composition comprising the antibody of claim 2. Claim 16 is directed to an immunoassay kit comprising the antibody of claim 2. Claims 9 and 11 are directed to methods for detecting Aβ11-x with the labelled antibody of claim 3. Claim 14 is directed to a method of diagnosis of disease associated with Aβ peptides with the labelled antibody of claim 3.

As stated in the response submitted October 15, 2007, none of the cited references disclose or teach an antibody with the immunoreactivity specific to Aβ11-x peptides and not to full length Aβ1-40/42 peptides. Briefly, Walker et al. discloses the monoclonal antibody 10D5, specific to Aβ1-16, which recognizes native Aβ. Pirttila et al. discloses two monoclonal antibodies 4G8, specific to Aβ17-24, and 6E10, specific to Aβ1-16. Both antibodies recognize soluble Aβ peptides. WO200162801 discloses the humanized

antibody 266 with specificity to an epitope contained within position 13-28 of Aβ and the use of the antibody 266 to bind and sequester Aβ40 peptide. Naslund et al. discloses the use of monoclonal antibody 6E10 to determine structures and abundances of Aβ variants.

The Office does not consider that the differences in the cross-reactivity to Aβ1-40/42 is significant, and alleges that the claimed antibodies have the same function, property or characteristics as the antibodies in the cited references. Also, the Office alleges that since the epitope of the claimed antibodies is present in the disclosed antibodies, the disclosed antibodies would inherently bind to Aβ11-17 and 11-15 as claimed. See Office Action, page 4.

Applicants respectfully submit that the function, property, and characteristics of antibodies depend on several factors, including binding specificity, affinity, and cross reactity. Such features are commonly recognized in the art and are shown by the following excerpt: "Antigen-antibody reaction can show a high level of specificity, that is, the binding sites of antibodies directed against determinants on one antigen are not complementary to determinants of another antigen...The specificity of an antiserum is the result of the summation of actions of the various antibodies in the total population each reacting with a different part of the antigen molecule and even different parts of the same determinant. However, when some of the determinants of an antigen A, are shared by another antigen B, then a proportion of the antibodies directed to A will also react with B. This is termed cross-reactivity. *The speficity and cross-reactivity expressed by an antiserum are properties which result from the antibody molecules within the serum.*" Emphasis added. See Immunology by I. Roitt, J. Brostoff, D. Male, which is submitted herein. As the cross-reactivity is a property of any given antibody; the claimed antibodies, with specificity to Aβ11-x and no cross-reactivity to Aβ1-40/42, should not be considered to be "inherent" or have the same function as antibodies which have cross-reactivity to Aβ1-40/42.

Applicants also submit that the epitopes of Aβ11-15 and Aβ11-17 are not necessarily encompassed within the epitopes of 10D5 (Aβ1-16), 6E10 (Aβ1-16), 4G8 (17-24), 266 (13-28). As shown in the above excerpt, the same determinant of the antigen likely gives rise to more than one antibody and these resulting antibodies may not

bind or correspond to the same determinant, i.e., epitope. For example, the 4G8 antibody is raised against Aβ17-24 and its epitope lies within Aβ18-22 (VFFAE), whereas the 6E10 antibody is raised against Aβ1-16 and its epitope lies within Aβ4-9 (FRHDSG). See the information from the supplier's website, sumbitted herein. Clearly, neither the Aβ18-22 epitope of the 4G8 antibody nor the Aβ4-9 epitope of the 6E10 antibody are encompassed within Aβ11-15/17. Therefore, the antibodies of the above references do not inherently bind to Aβ11-17 and 11-15.

The cited references do not anticipate the monoclonal antibody recited in the claims. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102 are respectfully requested.

B. Claims 2, 5, 8 and 14-16 are rejected under 35 U.S.C. § 102(a)/(b)

Claims 2, 5, 8, 14-16 are rejected under 35 U.S.C. §102 as alleged being anticipated by Solomon et al. 1996, and as being anticipated by Huse et al. 2002. The Examiner alleges that Solomon et al., which discloses antibodies against Aβ1-28 and Aβ8-17, inherently recognizes Aβ11-x as the sequence of the immunogens are encompassed in Aβ1-28 and Aβ8-17, and that Huse et al., which discloses BNT77 specific to Aβ11-16, recognizes N-terminal truncated Aβ peptides.

Solomon et al. discloses antibodies AMY-33 and 6F/3D, which are specific to Aβ1-28 and Aβ8-17, respectively. Both antibodies recognize and form immunocomplexes with synthetic Aβ1-40. Solomon et al. does not disclose an antibody with specificity to Aβ11-x and no cross-reactivity to full-length Aβ1-40/42.

Huse et al. discloses several antibodies to examine Aβ and APP species. Only antibodies BAN50, BNT77 and 4G8, which recognize the N-terminus of Aβ peptides are discussed herein. The BAN50 antibody, which is specific to Aβ1-10, is used to capture Aβ1-40/42 and the antibody BNT77, which is specific to Aβ11-16, is used to detect N-terminal truncated species and full-length Aβ peptide. Huse et al. also employs the

antibody 4G8 to immunoprecipate Aβ1-40, Aβ11-40, Aβ1-34 and Aβ11-34 peptides. Huse et al. does not disclose an antibody with specificity to Aβ11-x and no cross-reactivity to full-length Aβ1-40/42.

The cited references do not anticipate the monoclonal antibody recited in the claims. Reconsideration and withdrawal of the rejection under 37 U.S.C. § 102 are respectfully requested.

C. Claims 2-5, 8, 9, 11 and 14-16 are rejected under 35 U.S.C. § 103(a)

Claims 2-5, 8, 9, 11 and 14-16 are rejected under U.S.C. §103 over Huse et al. 2002 in view of Walker et al. 1994 and WO200162801. Specifically, the Examiner asserts that the antibodies disclosed in these references have the same properties as the claimed antibodies and that WO0162801 teaches the method of detecting Aβ in the brain tissue.

As discussed above, Huse et al., Walker et al., and WO200162801 do not disclose or suggest an antibody with specificity to Aβ11-x and no cross-reactivity to full-length Aβ1-40/42. Reconsideration and withdrawal of the rejection of claims 2-5, 8, 9, 11 and 14-16 under 35 U.S.C. § 103 are respectfully requested.

II. New Claim Objection

Claims 3, 5, 6, 8, 14 and 15 are objected to for the dependency on canceled claim 1. Applicants have amended these claims to recite "antibody as claimed in claim 2" to obviate any basis for this objection.

Reconsideration and withdrawal of the objection are respectfully requested.

III. New Rejections Under 35 U.S.C. § 112, first paragraph

Claims 14 and 16 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement with regard to diagnosing amyloid-related diseases with Aβ11-40 peptides. Applicants submit that amendment to the claims obviates any basis for the rejection.

IV. New Rejections Under 35 U.S.C. § 112, second paragraph

Claims 3-6, 14 and 16 are rejected under 35 U.S.C. § 112, second paragraph. Applicants submit that amendment to the claims obviates any basis for the rejection.

V. New Rejections Under 35 U.S.C. § 102 or 103

Claims 2, 6, 7 and 15-16 are rejected under 35 U.S.C. § 102 or 103. The examiner relies on U.S. Patent No. 6,984,720 for teaching a monoclonal antibody produced by a hybridoma cell line 5C4 that blocks amyloid accumulation in Alzheimer's patients. See Office Action, page 12.

The '720 patent is directed to human sequence antibodies that specifically bind to human CTLA-4, a T cell surface molecule. See Abstract and Column 3, line 8. The CTLA-4 antibodies stimulate the immune responses by blocking the binding of human CTLA-4 to human B7 for treating cancer and diseases associated with auto-antigens, such as Alzheimer's disease, and inflammatory component. See Column 9, lines 47-57. These antibodies to CTLA-4 can be produced by hybridoma cell lines, including 5C4. See Column 7, lines 41-51.

Although the term "5C4" is used in the '720 patent and in the present application, the 5C4 in the '720 patent is not the same as the 5C4 in the present application. The 5C4 line in the '720 patent produces antibodies specific to CTLA-4, whereas the 5C4 line in the present application produces antibodies specific to Aβ11-x peptides. Therefore the '720 patent does not teach the monoclonal antibodies that specifically recognize Aβ11-x

peptides as set forth in claim 2 nor the hybridoma cells J&JPRD/hAβ11/1 and J&JPRD/hAβ11/2 as set forth in claim 7.

Reconsideration and withdrawal of the rejection are respectfully requested.

VI. New Rejections Under 35 U.S.C. § 103(a)

Claims 2-11 and 14-16 are rejected as being unpatentable over Huse et al. 2002 in view of Walker et al. 1994 and WO200162801, and further in view of the '720 patent. As discussed above, Huse et al., Walker et al., and WO200162801 do not disclose or suggest the antibodies that specifically recognize Aβ11-15/17 with binding specificity to Aβ11-x peptides but not to full-length Aβ1-40/42 peptides as recited in the claims. Also as discussed above, the '720 patent does not disclose or suggest the hybridoma cell lines J&JPRD/hAβ11/1 and J&JPRD/hAβ11/2 as recited in the claims.

Reconsideration and withdrawal of the rejection are respectfully requested.

III. CONCLUSION

Early consideration and prompt allowance of the claims are respectfully requested. Should the Office require anything further, it is invited to contact applicants' representative at the telephone number below.

Respectfully submitted,

Date: June 2, 2008

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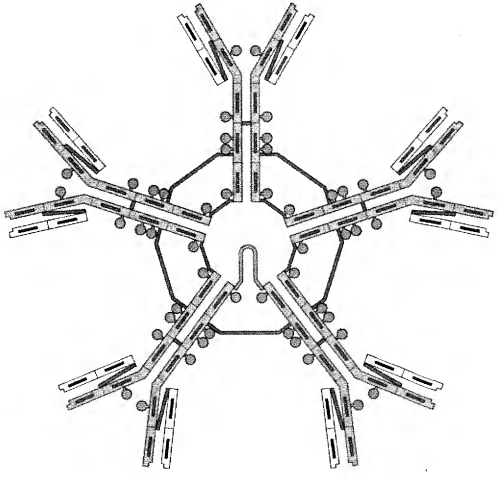
LD/YD
Attachments -
Immunology excerpt

IMMUNOLOGY

Ivan Roitt Jonathan Brostoff David Male



IMMUNOLOGY

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Many molecules however, have more than one antigenic determinant. Microorganisms have a very large number of antigenic determinants exposed on their surfaces, hence all these are multivalent. When a multivalent antigen combines with more than one of an antibody's combining sites, the binding energy between the two is considerably greater than the sum of the binding energies of the individual sites involved since all the antigen-antibody bonds must be broken simultaneously before the antigen and antibody will dissociate.

The strength with which a multivalent antibody binds a multivalent antigen is termed *avidity* to differentiate it from the *affinity* of the bond between a single antigenic determinant and an individual combining site. Thus the avidity of an antibody for its antigen is dependent on the affinities of the individual combining sites for the determinants on the antigen, but is greater than the sum of these affinities if both antigen and antibody are multivalent (Fig. 6.6). In normal physiological situations avidity is likely to be more relevant since naturally occurring antigens are multivalent; however, the precise measurement of hapten-antibody reactions is more likely to give an insight into the immunochemical nature of the antigen-antibody reaction.

ANTIBODY SPECIFICITY

Antigen-antibody reactions can show a high level of specificity, that is, the binding sites of antibodies directed against determinants on one antigen are not complementary to determinants of another antigen. For example, antibodies to a virus like measles will bind to the measles virus and confer immunity to this disease, but will not combine with, or protect against, an unrelated virus such as polio. The specificity of an antiserum is the result of the summation of actions of the various antibodies in the total population each reacting with a different part of the antigen molecule and even different parts of the same determinant (Fig. 6.7). However, when some of the determinants of an antigen, A, are shared by another antigen, B,

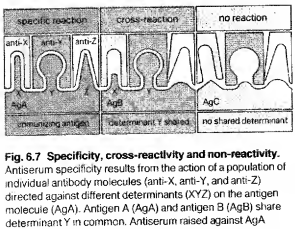

Fig. 6.7 Specificity, cross-reactivity and non-reactivity. Antiserum specificity results from the action of a population of individual antibody molecules (anti-X, anti-Y, and anti-Z) directed against different determinants (XYZ) on the antigen molecule (AgA). Antigen A (AgA) and antigen B (AgB) share determinant Y in common. Antiserum raised against AgA (anti-XYZ) not only reacts *specifically* with AgA but *cross-reacts* with AgB (through recognition of shared determinant Y and weak recognition of determinant X'). The antiserum gives *no reaction* with AgC (no shared determinants).

then a proportion of the antibodies directed to A will also react with B. This is termed *cross-reactivity*. The specificity and cross-reactivity expressed by an antiserum are properties which result from the antibody molecules within the serum.

Radical (R)	sulphonate	arsonate	carboxylate
	tetrahedral	tetrahedral	planar
ortho	+ +	−	−
meta	+ + +	+	±
para	±	−	−

Fig. 6.8 An example of specificity and cross-reactivity: recognition by antibody of overall antigenic structure rather than chemical composition. An antiserum is raised to the meta isomer of amino benzene sulphonate (the immunizing antigen). This antiserum is then reacted with the ortho and para isomers of amino benzene sulphonate and also with the three isomers (ortho, meta, para) of two different but related antigens: aminobenzene arsonate and amino benzene carboxylate. The antiserum reacts specifically with the sulphonate group (which has a tetrahedral structure) in the meta position but will give a cross-reaction (though weaker) with sulphonate in the ortho position. Further, but weaker, cross-reactions are possible when this antiserum is reacted with either the tetrahedral arsonate group or the planar carboxylate group in the meta, but not in the ortho or para position. The arsonate group is larger than sulphonate and has an extra H atom, while the carboxylate is smaller and planar. These results suggest that the overall configuration of the antigen is as important as individual chemical groupings.

There is evidence that the antibody recognizes the overall configuration of the antigen rather than its chemical composition and it is envisaged that antibodies are directed against particular three-dimensional electron cloud shapes rather than specific chemical structures (Fig. 6.8). In addition, there is frequently an inverse relationship between the charge of an antigen and the antibodies it induces (Fig. 6.9).

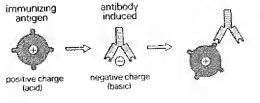

Fig. 6.9 Charge specificity. Antigen induces formation of, and complexes with, antibody of a charge opposite to its own.